Consequences of Preeclampsia (PE) for Offspring do not Increase with the Introduction of a Walking Intervention During Pregnancy

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CHAPTER I: Statement of the Problem

Background

During pregnancy, profound physiologic adaptations occur to preserve the maternal homeostasis while providing for fetal growth (Duvekot, 1994). Adaptations in the cardiovascular system and in metabolic processes yield the appropriate adaptive outcomes of increased blood volume, insulin resistance, and altered lipid metabolism. For most women, systemic circulatory and metabolic responses to pregnancy are tolerated uneventfully. For women who exhibit risk factors for metabolic or vascular disorders, these "physiologic" changes may induce a stress that results in an aberrant response during pregnancy.

Preeclampsia, a multisystem disorder, is one of the aberrant responses that can occur during pregnancy, and is usually identified in the third trimester of pregnancy. Typically, preeclampsia is diagnosed by the occurrence of three major signs (a) resting blood pressure of ≥140/90 mmHg, or an increase in systolic blood pressure of >30 mmHg, or >15 mmHg in diastolic blood pressure compared to an average of values prior to 20 weeks of gestation, (b) proteinuria >300 mg/24 hours, and (c) edema (Gifford, 1990). Data have shown that preeclampsia occurs at a rate of 6% in women during their first pregnancy (Sibai, 1993). However, 20% of women with preeclampsia during their first pregnancy will have preeclampsia recur during subsequent pregnancies. It is this group of women that are of particular concern, as women who experience recurrent preeclampsia are at increased risk of cardiovascular disease in later life. Therefore, it is important to develop interventions to prevent the recurrence of this condition and to understand the potential mechanisms of this condition.

The increased risk of cardiovascular disease may be a result of the hypertensive response seen in women with preeclampsia, as well as alterations in lipid metabolism that are common in

these women (Potter et al, 1979). For example, women with preeclampsia often have elevated triglyceride, low density lipoprotein (LDL), and free fatty acid concentrations. In addition, there is typically a reduction in high-density lipoprotein (HDL) and an increase in markers of oxidative stress (Hubel, 1996). Despite many theories as to the cause of preeclampsia, these characteristics suggest that endothelial activation is a common pathway for the development of this condition (Friedman, 1991).

Numerous studies have shown that exercise and an active lifestyle are inversely associated with morbidity and mortality from cardiovascular disease and related conditions. As a result, it is recommended that all individuals participate in 30 minutes of moderate intensity exercise 3-5 days of the week (Pate, 1995). During pregnancy, exercise has been shown to improve glucose control, and minimize the need for insulin in women with gestational diabetes (Bung, 1991). Moreover, it has been shown that pregnancy complications associated with cardiovascular and metabolic endpoints tend to occur in women who are unfit and sedentary (Knuist, 1998). Therefore, exercise may be an effective intervention strategy for preventing the recurrence of preeclampsia during pregnancy. However, the effectiveness of an exercise intervention during pregnancy for preventing the recurrence of preeclampsia in previously sedentary women has not been systematically examined.

Worldwide, preeclampsia is responsible for up to 20% of the 13 million preterm births and 15% of the 30 million growth restricted babies each year. The disease process of PE causes restricted growth because of the reduced blood flow to the placenta, and contributes to infant prematurity due to early delivery of the infant to end the high-risk PE consequences. Although exercise during pregnancy may be important for the health and well-being of the mother, the effects of exercise on the fetus have not been evaluated in at-risk pregnancy situations.

Therefore, a secondary analysis of data from a recent clinical trial was conducted to assess exercise on the fetus in a high-risk pregnancy. The aim of this clinical trial was to reduce the reoccurrence of PE in a later pregnancy, which is estimated to be about 20%. One hundred twenty-three women were enrolled in the study and these participants were randomized to a walking intervention (n=62) or to an attention-control group (n=61). The study had two aims. The first aim was that 30 minutes of moderate intensity physical activity performed 5 days per week would significantly reduce the reoccurrence of preeclampsia in sedentary pregnant women. The second aim was women who are randomized to the exercise intervention would report greater participation in health promoting behaviors and greater exercise self-efficacy than women who are randomized to usual care. There are currently no data to suggest that exercise during pregnancy results in adverse outcomes for either the mother or the fetus. However, because exercise is a newly proposed therapeutic approach for the management of metabolic homeostasis during pregnancy, its efficacy in improving control and its safety for both mother and fetus must continue to be evaluated (Avery et al, 1997). The American College of Obstetricians and Gynecologists have concluded that women can derive health benefits from participation in regular exercise during pregnancy, and have developed exercise guidelines that should be followed during pregnancy (*Exercise during pregnancy and the postpartum period*, 1994). The emphasis of their statement is the safety of the mother and fetus; therefore, the American College of Sports Medicine (ACSM) developed guidelines for safe exercise practices. The ACSM provides guidelines for all five components of an exercise prescription, namely the mode, intensity, duration, frequency, and progression of physical activity (Mahler et al, 1995). Unfortunately, these statements do not address high-risk circumstances. Nevertheless, the clinical trial's participants followed these guidelines. In the end, the results from the study did

not show a significant difference in PE recurrence between the walking intervention and the control group. The rate of reoccurrence of PE between both groups was not found to be significantly different. Newborn outcome variable, such as birth weight and weeks gestation at delivery were obtained, but not previously analyzed. These data can be used to address concerns raised for the well-being of the fetus due to the exercise.

Study Aims

This secondary analysis provides information about the effect of a clinical trial's walking intervention on the health of the infant born to women with a high-risk pregnancy, such as preeclampsia. Therefore, the aims of our secondary analysis are to (1) explore the effects of the parent study's walking intervention on birth weight and (2) examine the infant birth weight born to women with or without PE reoccurrence relative to other known PE risk factors.

CHAPTER II: Literature Review

Preeclampsia and Cardiovascular Disease

Preeclampsia (PE), a hypertensive disorder of pregnancy, occurs primarily in women with the first pregnancy, however, in 20% of women diagnosed with preeclampsia, the disorder will recur with subsequent pregnancies (Caritis et al, 1998). While the pathophysiology of preeclampsia is not completely understood, there is concurrence that endothelial cell dysfunction, a pathway that is evident in cardiovascular disease, plays a role in this complication of pregnancy. For the subset of women who experience recurrent preeclampsia in subsequent pregnancies, there is an increased risk of cardiovascular disease (Chesley, 1980). Previous meta-analyses have reported that after PE, women have a doubled risk for developing CVD and more than tripled the risk for developing hypertension (HTN) (Bellamy et al, 2007); this association may be related to the PE induced endothelial damage. For example, a meta-analysis done by Brown in the Netherlands, found that women with a history of PE were at significantly increased odds of fatal or diagnosed CVD [odds ratio (OR) = 2.28, 95 % confidence interval (CI): 1.87, 2.78], cerebrovascular disease (OR = 1.76, 95 % CI 1.43, 2.21) and hypertension [relative risk (RR) = 3.13, 95 % CI 2.51, 3.89]. Thus, vascular changes and risk factors that predispose to preeclampsia seem to also predispose to cardiovascular disease in later life. Additionally, Preeclampsia increases a woman's long-term risk of vascular disease and/or death including chronic hypertension, myocardial infarction, heart failure, stroke, and venous thromboembolism. The literature suggests that maternity care providers may be unaware of this association (Leslie et al, 2016).

Preeclampsia is a major contributor to perinatal morbidity and mortality, as it accounts for 15% of preterm births, and a 5-fold increase in perinatal mortality rate (Goldenberg and

Rouse, 1998). Because of the health implications for both the mother and the fetus, it is important to examine potential therapies to prevent the onset and/or recurrence of preeclampsia in pregnant women.

Vascular change effects on endothelium

Evidence suggests that women who experience PE are at a greater risk for hypertension and heart disease later in life compared to normal pregnancies. A study done by Agatisa (2004) had the objective of determining whether endothelial function is impaired in postpartum women with a history of PE in their first pregnancy. They measured forearm blood flow (FBF) by venous occlusion plethysmography in 50 healthy women: 16 with prior PE, 14 with prior normotensive pregnancy, and 20 never pregnant controls. The researchers found that baseline FBF, HR, systolic BP, and diastolic BP did not significantly differ among the groups, whereas mean arterial pressure in the preeclamptic group was greater than that of the normal pregnancy group ($P = 0.03$). Stress-induced FBF (percent change over baseline) was reduced in the preeclamptic group compared with both the normal pregnancy and never pregnant groups ($P = 0.06$) and was significantly attenuated compared with women with prior normal pregnancies (91% vs. 147%, $P = 0.006$). These data demonstrate that women with a history of preeclampsia exhibit impaired endothelial function up to 1 yr. postpartum (Agatisa et al, 2004). This damage is thought to be a trigger for the formation of blood clotting, plaques, and atherosclerosis; additionally, endothelial tissue plays an important role in vasoconstriction and vasodilation, which ultimately impacts blood pressure (Lim et al, 2016). Overall, these observations may explain their increased risk for hypertension and cardiovascular disease

Exercise in Pregnancy

It is a known concept that exercise is good for one's health, so more recently, the effects of exercise during pregnancy have been studied. For example, a systematic review and meta-analysis (Magro-Malosso et al, 2017) analyzed the effect of exercise in women with gestational hypertensive disorders. The results showed that aerobic exercise for about 30-60 minutes 2-7 times per week during pregnancy, as compared to being more sedentary, is associated with significantly reduced risk of gestational hypertensive disorders. Furthermore, a paper in Clinical Obstetrics and Gynecology (Magro-Malosso et al, 2017) provided an overview of the current understanding of these physiological adaptations to acute prenatal exercise. When a woman who is pregnant exercises, her heart rate rises and the resting stroke volume increases until the second trimester before declining towards prepregnancy levels before birth. The etiology of the decreased rate is likely due to the elevated bioavailability of nitric oxide and sympathetic vasoconstrictor responsiveness. The increase in stroke volume occurs as a result of the increased blood volume during gestation—an elevated preload. Together with an elevated heart rate, this contributes to a significantly higher cardiac output (30%) in pregnancy women during the third trimester (Davenport, 2016). Therefore, the progressive increase of blood volume and cardiac output subsequently contribute to the increase in blood pressure observed later in pregnancy; the increased blood pressure that accompanies exercise in women with hypertensive pregnancy disorders is an important factor that needs further research. An additional area of limited information is the maternal peripheral hemodynamics during pregnancy. During exercise, there is an augmented stroke volume response to accommodate the larger cardiac output; however, the distribution of the cardiac output is less well known (Davenport, 2016). Thus, additional research on this blood distribution during exercise in pregnancy and its effects on the fetus are warranted.

Chapter Summary

Preeclampsia, a hypertensive disorder of pregnancy, creates an increased risk in women for developing hypertension and cardiovascular disease (Bellamy et al, 2007); this association may be related to the PE-induced endothelial damage. Due to the health implications for both the mother and the fetus, it is important to examine potential therapies to prevent the onset and/or recurrence of this disease process for expecting mothers. Aerobic exercise for about 30-60 minutes 2-7 times per week during pregnancy, as compared to being more sedentary, is associated with significantly reduced risk of gestational hypertensive disorders**.** Further research is needed to assess how exercise influences the fetus's well-being and development, especially in women with gestational hypertensive disorders.

CHAPTER III: Methodology

Research Design

This descriptive study used data collected in a randomized controlled study entitled, *Exercise Intervention to Reduce Recurrent Preeclampsia* (R01NR05275). In that study, a group of pregnant women with a history of preeclampsia were randomized to a walking intervention group or an attention control group to determine if increasing exercise during pregnancy could reduce the rate of reoccurring preeclampsia. Subjects were instructed to exercise for 10 minutes, 3 times per day for at least 5 days per week**.** The general instruction for exercise was for the participant to walk briskly, yet comfortably, for the 10-minute duration; additionally, participants kept daily personal records of the date, time of day, duration of time walked. To assure compliance with the protocol, exercise sessions were monitored at random by asking the subject to wear a pedometer to assess distance walked. In addition, subjects were randomly selected to walk with a research staff member. This observation allowed for confirmation of the subjects perceived exertion and tolerance of exercise.

Behavioral and clinical data were obtained at three points throughout pregnancy and analyzed to compare the metabolic changes that the women in the control and intervention group underwent throughout their pregnancy. Furthermore the criterion in Table 1 below was used to determine the presence of PE after the implementation of the trial's walking intervention.

Table 1

Criteria for assessing for recurrence of Preeclampsia

	Blood Pressure	Urinary Protein	Uric Acid
Recurrence of Preeclampsia	Elevated blood pressure (at least two readings fulfilling criteria) that returns to normal by 12 weeks postpartum.	Dipstick of random urine with $\geq$2+ on voided or $\geq$1+ on catheterized random specimen	Hyperuricemia ($\geq$ 1 S.D. above the mean for

	≥30mm Hg change in sBP *or* ≥15 mm Hg in dBP from baseline* OR sBP ≥140 mm Hg or dBP ≥90 mm Hg if no baseline measurement	≥0.5 g of protein in a 24 hour urine collection	gestational age)
No recurrence, uncomplicated pregnancy	< 30 mm Hg change in sBP and <15 mm Hg in dBP from baseline OR sBP < 140 mm Hg and dBP < 90 mm Hg if no baseline measurement	All dipsticks of random urine with <2+ on voided and <1+ on catheterized random specimens <0.3 g of protein in all 24 hour urine collections	Hyperuricemia (< 1 S.D. above the mean for gestational age)

Population Sample

Participants of the original study were recruited from an urban hospital in the Northeastern United States. All participants were pregnant, had a history of preeclampsia with the same partner, and self-reported a sedentary lifestyle. Individuals were excluded from the study if there was found to be an existing medical condition present that increased the risk for developing preeclampsia such as hypertension, diabetes, multiple gestation, or if the woman had a history of more than one prior preeclamptic pregnancy as this would increase the likelihood of recurring preeclampsia and act as a confounding factors to the study's results.

One hundred twenty-three women participated in the parent study. Of those women, 88 were included in this secondary analysis, based on the availability of birth data needed for the analysis of infant outcomes.

Maternal and Infant Variables

Following identification of women for the secondary analysis, outcome data such as such as recurrence of preeclampsia, race and age of the mother, infant gestational age at birth, and infant birth weight were abstracted from the de-identified research record.

Data Analysis

Data were entered into a relational database and exported to the Statistical Program for the Social Sciences (SPSS). Descriptive and inferential statistics were used to (1) describe the sample and the maternal and infant outcomes of interest, (2) examine the birth weight for infants born to women with or without PE recurrence relative to other known PE risk factors.

Chapter IV: Research Results

The aims of our secondary analysis were to (1) explore the effects of the parent study's effect of walking intervention on birth weight and (2) examine the infant birth weight born to women with or without PE reoccurrence relative to other known PE risk factors.

The demographics of the sample are represented in Table 2 below for the 88 participants by group allocation to depict the similarity of characteristics of each group.

Table 2

Demographics of participants (n=88)

	Walker	Control
Number of participants	42	46
Number who developed preeclampsia	2	7
White race	38 (43.18%)	35 (39.77%)
Age of participants	29.48 ± 5.07	29.48 ± 5.02
Weeks gestation at birth	38.07 ± 2.05	38.51 ± 1.73

In regards to our first aim, infants born to women in the walking group had a mean birth weight (± standard deviation) of 3382.95 grams ± 585.03 grams, as compared to the mean birth weight of 3402.50 grams ± 583.21 grams for the control group. This information is shown in Table 3 below. There are no differences in birth weight between the two groups, as the significance is 0.924.

Table 3

Group Statistics

	Group	N	Mean (g)	Std. deviation (g)	Std. Error Mean (g)
Birth weight (grams)	C	44	3402.50	583.208	87.922
	W	41	3382.95	585.041	91.368

The second aim's results looked more specifically at the difference in week's gestation between the women with PE and women without PE. Women with preeclampsia gave birth significantly earlier than women who did not experience PE (p=0.00).

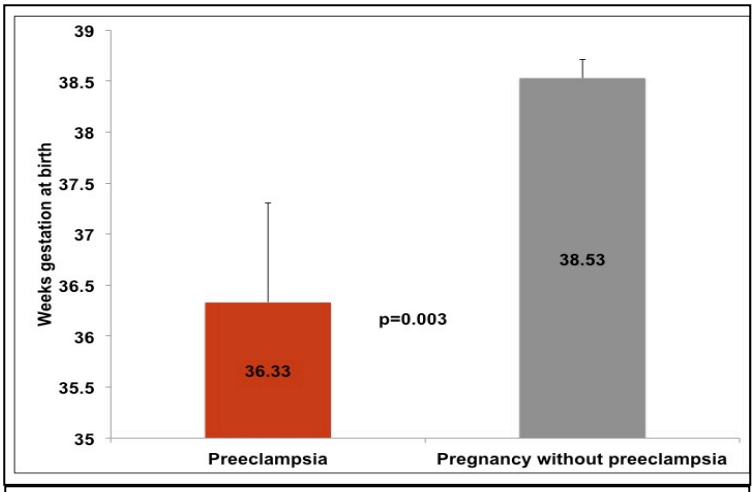

Figure 1: Weeks of gestation of baby in women with or without preeclampsia

The other component of the second aim analyzed birth weight in grams of the infants born to women with PE compared to women without PE during pregnancy. The results showed that infants born to women with preeclampsia had a significantly lower birth weight as compared to infants born to women without PE.

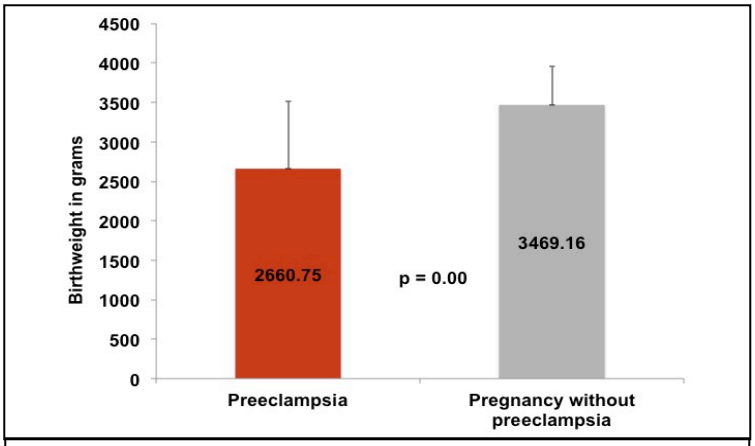

Figure 2. Birth weight (g) of baby born to women with or without preeclampsia.

Overall, the women with PE had a shorter gestational period and birthed infants of lesser birth weight in grams. There is a strong positive correlation between week's gestation and birth weight, indicating that longer gestation is important for fetal growth.

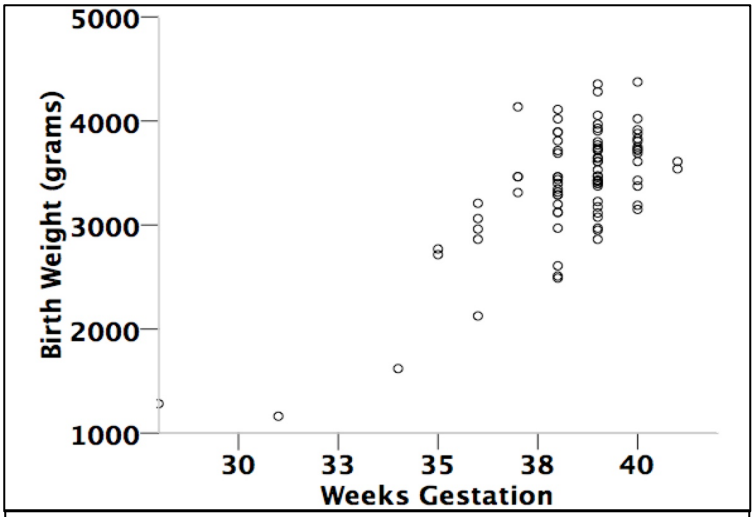

Figure 3. Birth weight (grams) of infants in relation to gestation (weeks).

Chapter V: Discussion/Implications

Thus, the birth weights of infants in the walking (3382.95 grams ± 585.03 grams) and control groups (3402.50 grams ± 583.21 grams) were quite similar, as the significance between the two was 0.924. This indicates that the exercise intervention used in the study did not place the infants at risk, and verifies the potential benefit of exercise for pregnant women—including those women who experience a high-risk pregnancy, such as preeclampsia. Furthermore, the results showed that infants born to women with preeclampsia experience a shorter gestational age (36.33 weeks gestation) and lower birth weight (2660.75 grams) both of which are effects of the maternal disease vascular changes; therefore, infants of PE mothers are at an immediate health risk as soon as they are born. Additionally, there was a significant correlation between week's gestation at birth and birth weight ($r=0.72$, $p=.00$), indicating that the weights were appropriate for gestational age and consistent with expectations.

A shorter gestational age and lower birth weight were expected as these are common for women with preeclampsia. A woman with PE has to deliver her child early in order for the disease process symptoms to end. As discussed earlier, the hypertensive nature of preeclampsia can be fatal to the mother if untreated. Research regarding an alternative treatment for terminating the PE disease process without prematurely delivering the baby is recommended. Our suggestions to accomplish this include prescreening, a nutritional supplement to the baby to support growth despite an early delivery and low birth weight, or pharmacological interventions—either while in utero or postpartum.

In conclusion, this study demonstrates that the walking intervention did not have detrimental effects on offspring. The benefits of exercise on the mother's health and well-being cannot be understated. Although the overall results of this trial were negative in preventing PE, a

larger trial testing other forms of exercise in women with a high-risk pregnancy might be warranted.

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